Characteristics and outcomes of patients enrolled in the CORRECT and CONCUR phase 3 trials of regorafenib for metastatic colorectal cancer (mCRC)

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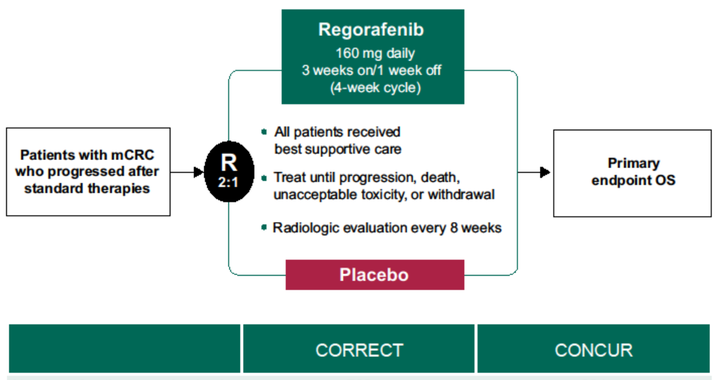
BACKGROUND

- Regorafenib is an oral multikinase inhibitor that blocks the activity of multiple protein kinases involved in the regulation of oncogenesis, angiogenesis, and the tumor microenvironment[1]
- The international phase 3 CORRECT trial (NCT01103323) showed that regorafenib improves overall survival (OS) versus placebo in patients with previously treated mCRC[2]
- The phase 3 CONCUR trial (NCT01584830) confirmed the OS benefit for regorafenib in Asian patients[3]
- We examined the characteristics of patients and the efficacy and safety outcomes in the two trials

METHODS

- The study designs of the CORRECT and CONCUR trials were similar (Figure 1)
  - Patients in CORRECT were required to have had prior targeted biological treatment; in CONCUR, prior targeted biological treatment was allowed, but not required

Figure 1: ***CORRECT and CONCUR study designs[2,3]***



	CORRECT	CONCUR
Number of patients randomized	760	204
Enrollment	16 countries in Europe, North-America, Asia-Pacific region, rest of the world	China, Hong Kong, Taiwan, South Korea, Vietnam
Prior targeted biologic therapy: bevacizumab; cetuximab/ panitumumab (*KRAS* wild-type)	Required	Allowed, **but not required**
Primary analysis of OS (assumed 33.3% improvement; HR 0.75 favoring regorafenib)	One-sided alpha 0.025 90% power	One-sided alpha 0.20 80% power
Stratification factors for randomization	Previous treatment with VEGF-targeting drugs; time from mCRC diagnosis (≥18 vs <18 months); geographic region	Number of metastatic sites (single vs multiple); time from mCRC diagnosis (≥18 vs <18 months)

HR, hazard ratio; mCRC, metastatic colorectal cancer; OS, overall survival; R, randomization; VEGF, vascular endothelial growth factor.

RESULTS

Baseline characteristics

- A higher proportion of patients in CORRECT than in CONCUR had >3 prior treatment lines for metastatic disease (Table 1)
- In CONCUR, approximately 60% of patients had prior targeted biological treatment compared with 100% of patients in CORRECT

Table 1: ***Baseline characteristics[2,3]***

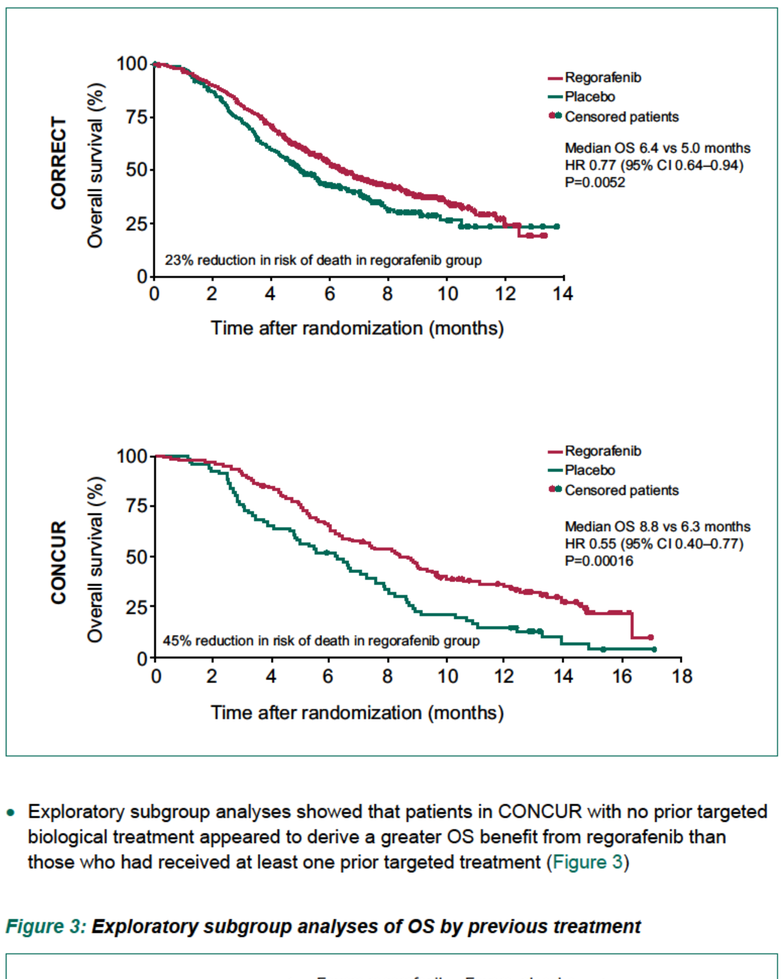
	CORRECT		CONCUR	
	Regorafenib (n=505)	Placebo (n=255)	Regorafenib (n=136)	Placebo (n=68)
Median age, years (IQR)	61 (54–67)	61 (54–68)	58 (50–66)	56 (49–62)
Male, %	62	60	63	49
Race, % Asian	15	14	100	100
Median body mass index, kg/m²	25	26	23	23
ECOG PS 0/1, %	52/48	57/43	26/74	22/78
KRAS wild-type/mutant/unknown, %	41/54/5	37/62/2	37/34/29	43/26/31
>3 prior treatment lines for metastatic disease, %	**49**	**47**	**38**	**40**
Previous targeted biological treatment, %				
None	0	0	**41**	**38**
Any (anti-VEGF, anti-EGFR, or both)	100	100	59	62
Anti-VEGF, but not anti-EGFR	48	52	24	19
Anti-EGFR, but not anti-VEGF	0	0	18	25
Anti-VEGF and anti-EGFR	52	48	18	18

ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; IQR, interquartile range; VEGF, vascular endothelial growth factor.

Overall survival

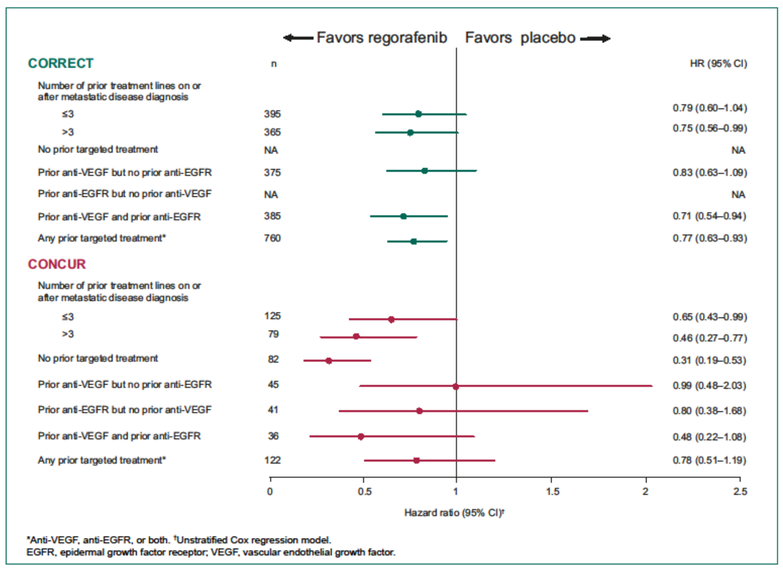
- Regorafenib significantly improved OS versus placebo in both CORRECT and CONCUR (Figure 2)[2,3]

Figure 2: ***Kaplan–Meier analyses of OS[2,3]***



- Exploratory subgroup analyses showed that patients in CONCUR with no prior targeted biological treatment appeared to derive a greater OS benefit from regorafenib than those who had received at least one prior targeted treatment (Figure 3)

Figure 3: ***Exploratory subgroup analyses of OS by previous treatment***



*Anti-VEGF, anti-EGFR, or both. †Unstratified Cox regression model.
EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor.

Progression-free survival

- Regorafenib significantly improved progression-free survival (PFS) versus placebo in both CORRECT and CONCUR[2,3]
  - CORRECT: median PFS 1.9 months versus 1.7 months
- HR 0.49 (95% CI 0.42–0.58); one-sided P<0.0001
  - CONCUR: median PFS 3.2 months versus 1.7 months
- HR 0.31 (95% CI 0.22–0.44); one-sided P<0.0001

Tumor response

- In both trials, the proportion of patients who achieved disease control was higher in the regorafenib group than in the placebo group (CORRECT 41% vs 15%; CONCUR 51% vs 7%, respectively; P<0.0001 for both comparisons)
- The objective response rate (complete plus partial response; regorafenib vs placebo) was 1% versus <1% in CORRECT and 4% versus 0% in CONCUR

Safety

- In both studies, median duration of treatment was longer for regorafenib than for placebo
  - CORRECT: regorafenib 1.7 months; placebo 1.6 months
  - CONCUR: regorafenib 2.4 months; placebo 1.6 months
- Mean (standard deviation) daily dose of study drug was as follows:
  - CORRECT: regorafenib 147.1 mg (18.6); placebo 159.2 mg (4.9)
  - CONCUR: regorafenib 145.4 mg (18.1); placebo 160 mg (0)
- In both trials, approximately 40% of regorafenib-treated patients had adverse events leading to dose reduction (Table 2)
- Grade ≥3 regorafenib-related hand–foot skin reaction occurred in 17% of patients in CORRECT and 16% of patients in CONCUR (Table 3)
- Grade 3 or 4 hepatic and hematologic laboratory abnormalities of interest, regardless of relation to study drug, are shown in Table 4

Table 2: ***Treatment-emergent adverse events*[2,3]***

Proportion of patients (%)	CORRECT†		CONCUR†	
	Regorafenib (n=500)‡	Placebo (n=253)‡	Regorafenib (n=136)	Placebo (n=68)
Any grade, regardless of relationship to study drug	100	97	100	88
Grade ≥3	78	49	71	44
Serious	44	40	32	26
Grade 5	13	15	9	10
Leading to treatment discontinuation	18	13	14	6
Leading to dose reduction	38	3	40	0
Leading to treatment interruption	61	22	63	16
Any grade, drug-related	93	61	97	46
Grade ≥3	55	14	54	15

*During treatment or up to 30 days post treatment.
†Adverse events were graded using the NCI-CTC for Adverse Events version 3.0 (CORRECT) and version 4.0 (CONCUR).
‡Safety analyses are based on 753 patients who initiated treatment.

Table 3: ***Selected drug-related grade ≥3 adverse events[2,3]***

Proportion of patients (%)	CORRECT†		CONCUR†	
	Regorafenib (n=500)‡	Placebo (n=253)‡	Regorafenib (n=136)	Placebo (n=68)
Hand–foot skin reaction	17	<1	16	0
Fatigue	10	5	3	1
Hypertension	7	1	11	3
Diarrhea	7	1	1	1
Hypophosphatemia	4	<1	7	0
Lipase increase	3	<1	4	1
Rash	6	0	4	0

†Adverse events were graded using the NCI-CTC for Adverse Events version 3.0 (CORRECT) and version 4.0 (CONCUR).
‡Safety analyses are based on 753 patients who initiated treatment.

Table 4: ***Treatment-emergent hepatic and hematologic laboratory values of interest, regardless of relation to study drug***

Proportion of patients (%)	CORRECT		CONCUR	
	Regorafenib	Placebo	Regorafenib	Placebo
ALT increased				
Grade 3	5	3	9	1
Grade 4	<1	<1	0	0
AST increased				
Grade 3	5	4	10	3
Grade 4	<1	<1	<1	0
Blood bilirubin increased				
Grade 3	10	5	7	4
Grade 4	3	3	4	0
Anemia				
Grade 3	5	3	8	1
Grade 4	<1	0	0	0
Neutropenia				
Grade 3	<1	0	3	0
Grade 4	0	0	1	0
Thrombocytopenia				
Grade 3	2	<1	3	0
Grade 4	<1	0	<1	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

CONCLUSIONS

- The international phase 3 CORRECT trial demonstrated the clinical benefit of regorafenib in patients with previously treated mCRC, and the results were confirmed by the phase 3 CONCUR trial[2,3]
  - Statistically significant improvements in OS compared with placebo were reported in both Asian and non-Asian populations
  - Regorafenib was also superior to placebo in analyses of PFS and disease control rate in both trials
- A subgroup analysis of OS in CONCUR showed that the benefit in patients who had received previous targeted treatment (HR 0.78 [95% CI 0.51–1.19]) was similar to that reported in CORRECT (HR 0.77 [95% CI 0.64–0.94]), in which all patients received at least one prior targeted therapy
- Adverse events were generally similar in the two trials and were consistent with the known safety profile of regorafenib
- These results confirm the role of regorafenib as an important treatment option for patients whose mCRC has progressed after standard treatments

References

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